Secretin

CLINICAL PHARMACOLOGY

The primary action of SecreFlo™ is to increase the volume and bicarbonate content of secreted pancreatic juices. The standard unit of activity used for SecreFlo™ is the clinical unit defined by Jorpes & Mutt in 1966.(1) In the validated cat bioassay, which was used to define and quantitate the biological activity of secretin and as the release test for the biologically derived porcine secretin product, SecreFlo™ demonstrates a potency of approximately 5000 clinical units (CU) per milligram of peptide as opposed to 3000 CU per mg for biologically derived porcine secretin. As a pure peptide drug product, SecreFlo™ dosing is expressed by weight in micrograms. The relationship of micrograms of secretin to biological activity is 0.2 mcg = 1 CU.

Pharmacokinetics: The PK profile for SecreFlo™ was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 mcg/kg, SecreFlo™ concentration rapidly declines to baseline secretin levels within 60 to 90 minutes in most of the normal volunteers studied. The elimination half-life of SecreFlo™ is 27 minutes. The clearance of SecreFlo™ is 487 ± 136 mL/minute and the volume of distribution is about 2 liters.

CLINICAL STUDIES

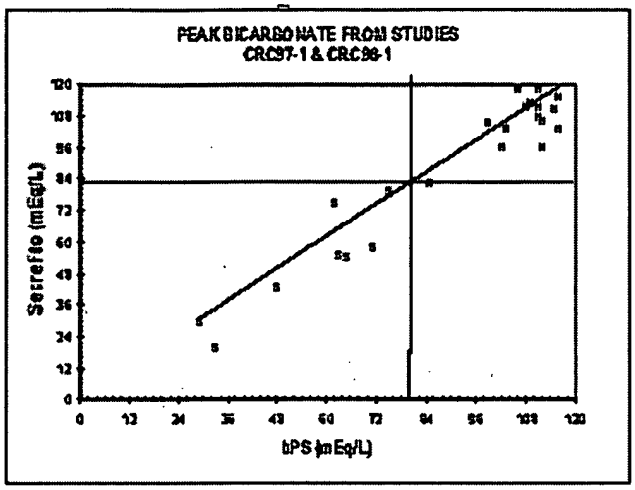
To stimulate pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreas dysfunction:

SecreFlo™ administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can assist in the diagnosis of exocrine pancreas dysfunction. Normal ranges for pancreatic secretory response to intravenous secretin in patients with defined pancreatic diseases have been shown to vary. One source of variation is related to the inter-investigator differences in operative technique.

Two small studies (CRC 97-1 and CRC 98-1) examined the relationship of peak bicarbonate concentration observed in three groups of patients: normal healthy subjects; patients with chronic pancreatitis; patients with a past medical history of chronic pancreatitis and abnormal secretin stimulation test results but with sufficient recovery of exocrine pancreas function to have currently normal test results (Figure 1). SecreFlo™ was compared to biologically derived porcine secretin (bPS). All 12 normal subjects had peak bicarbonate concentrations >80 mEq/L while all patients with chronic

pancreatitis had peak bicarbonate concentrations <80 mEq/L.

Figure 1



A 45 degree reference line: bPS = SecreFlo™
S = Sick patients
R = Recovered patients
H = Healthy subjects

The values obtained for Figure 1 were performed by investigators skilled in performing secretin stimulation testing and are to be taken only as guidelines. These results should not be generalized to results of secretin stimulation testing conducted in other laboratories. However, a volume response of less than 2.0 mL/kg/hr, bicarbonate concentration of less than 80 mEq/L, and bicarbonate output of less than 0.2 mEq/kg/hr are consistent with impaired pancreatic function.

A physician or institution planning to perform secretin stimulation testing for diagnosis of pancreatic disease should begin by assessing enough normal subjects (>5) to develop proficiency in proper techniques and to generate normal response ranges for the commonly assessed parameters of pancreatic exocrine response to SecreFlo™.

In three crossover studies (CRC 98-1, CRC 98-2, and CRC 99-9) evaluating 21 different patients with a documented history of chronic pancreatitis, SecreFlo™ was compared to biologically derived secretin (bPS). All of the patients, treated with either drug, had peak concentrations of <80 mEq/L. Proper technique for carrying out secretin stimulation testing is described in **DOSAGE AND ADMINISTRATION**.

Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma:

SecreFlo™ administered intravenously stimulates gastrin release in patients with gastrinoma whereas only small changes in serum gastrin concentrations occur in normal subjects and patients with peptic ulcer disease. Deveney et al.,1977[2] established secretin stimulation testing as an aid in the diagnosis of gastrinoma by using discriminant analysis. An increase from basal levels of ≥110 pg/mL was the optimal point separating positive and negative tests. This gastrin response is the basis for the use of secretin as a provocative test in the evaluation of patients in whom gastrinoma is a diagnostic consideration.

In two crossover studies, eight patients with tissue confirmed gastrinoma received SecreFlo™. Results of serum gastrin concentrations were compared with those for biologically derived porcine secretin. Serum gastrin concentrations exceeded 110 pg/mL from basal levels in all patients for both drugs tested.

Correlation with clinical data and additional diagnostic modalities should be utilized when considering the diagnosis of gastrinoma.

Proper technique for carrying out secretin stimulation testing is described in **DOSAGE AND ADMINISTRATION**.

Faciliation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts: In a randomized, placebo controlled crossover study in 31 patients with pancreas divisum undergoing ERCP, SecreFlo™ administration at a dose of 0.2 mcg/kg resulted in 25 of 28 successful cannulations of the minor duct compared to 1 of 16 for placebo.

REFERENCES

1. Jorpes, E. and Mutt V. On the biological assay of secretin. The reference standard. Acta Physiol Scand 66 (1966) 316-325.

2. Deveney, C.W., et al. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison Syndrome). Annals of Internal Medicine 87 (1977) 680-686.